EXHIBIT 4

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-553/S-058

INFORMATION REQUEST LETTER

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Beth Connelly
Assistant Director, U.S. Regulatory Affairs

Dear Ms. Connelly:

Please refer to your supplemental new drug application dated May 21, 2007, received May 22, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for OxyContin (Oxycodone Hydrochloride Extended-Release) Tablets.

We also refer to your submission dated February 14, 2008.

This supplemental new drug application proposes a risk management plan for OxyContin. We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. It will be necessary for you to submit a proposed Risk Evaluation and Mitigation Strategy (REMS) for the reasons described below in place of the risk management plan.

For administrative purposes, please withdraw your supplemental new drug application S-058 and submit a new supplement containing the proposed REMS.

RISK EVALUATION AND MITIGATION STRATEGIES (REMS) REQUIREMENTS

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize FDA to require the submission of a REMS for an approved drug if FDA becomes aware of new safety information and determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

Since OxyContin was approved on December 12, 1995, for the management of moderate to severe pain in patients where use of an opioid analgesic is indicated for more than a few days, we have become aware of postmarketing reports of overdose, abuse, and addiction associated with OxyContin. This information was not available when OxyContin was granted marketing

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authorization. Therefore, we consider this information to be "new safety information" as defined in FDAAA.

Based on this new safety information, and in accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for OxyContin to ensure that the benefits of the drug outweigh the risks of: 1) use of dosages 60 mg and above in non-opioid-tolerant individuals; 2) abuse; and 3) overdose, both accidental and intentional.

Your proposed REMS must contain the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Under 21 CFR Part 208 and in accordance with 505-1, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed OxyContin. Pursuant to 21 CFR Part 208, FDA has determined that OxyContin poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of OxyContin. FDA has determined that OxyContin is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use, or continue to use OxyContin. FDA has also determined that OxyContin is a product for which patient labeling could help prevent serious adverse events.

Elements to Assure Safe Use: We have determined that elements to assure safe use are necessary to mitigate serious risks listed in the labeling of the drug. In addition, we have determined that the Medication Guide discussed above is not sufficient to mitigate the serious risks. Your REMS must include tools to manage these risks, including at least the following:

1) A plan to ensure that Oxycontin will only be prescribed by prescribers who are specially certified under 505-1(f)(3)(A) through the certification process described below. At a minimum the plan shall require that:
   (a) Prescribers are trained about:
      (i) proper patient selection
      (ii) appropriate product dosing and administration,
      (iii) general opioid use including information about opioid abuse and how to identify patients who are at risk for addiction
      (iv) the risks of OxyContin including:
         1. the risk of overdose caused by exposure to an essentially immediate release form of oxycodone due to crushing, chewing or dissolving OxyContin
         2. The risk of addiction from exposure to OxyContin
      (v) how to enroll patients into the REMS program
   (b) Prescribers have obtained certification by attesting to the following:
      (i) I have been trained and understand the risks and benefits of chronic opioid therapy

(ii) I understand OxyContin can be abused and this should be considered when prescribing or dispensing OxyContin in situations where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.
(iii) I understand that OxyContin Tablets are indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.
(iv) I understand that OxyContin dosages of 60 mg and above are for use in opioid-tolerant patients only. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.
(v) I will prescribe OxyContin after ensuring documentation of safe use conditions described below.
(vi) I will enroll patients into the REMS program.

(c) The sponsor will maintain a list of the prescribers who have obtained the certification, and provide the list to those needing to verify that a prescriber has obtained the required certification.
(d) Prescribers will be retrained and recertified periodically, at a specified interval.

2) A plan to ensure that OxyContin is only dispensed by pharmacies, practitioners, or healthcare settings (e.g., hospitals) who are specially certified under 505-1(f)(3)(B) by requiring that:
(a) OxyContin is dispensed through certified pharmacies, practitioners, or healthcare settings. To obtain certification, a pharmacy, practitioner, or healthcare setting must agree to:
(i) Train their staff, including pharmacists and practitioners, about the REMS procedures and education materials
(ii) Dispense OxyContin after ensuring documentation of safe use conditions described below

(b) The sponsor will maintain a list of the pharmacies, practitioners, or healthcare settings who have obtained the certification, and provide the list to those needing to verify that the required certification has been obtained.
(c) Pharmacies, practitioners, or healthcare settings will be retrained and recertified periodically, at a specified interval.

3) A plan to ensure the drug is dispensed to patients with documentation of the following safe use conditions under 505-1(f)(3)(D):
(a) A prescriber must document that he or she:
(i) Has enrolled each patient by obtaining at the time of first prescribing and on a specified periodic frequency thereafter a signed physician-patient agreement form that documents safe use conditions, i.e., patients being prescribed the higher doses (i.e., 60 mg and above) are opioid tolerant; patients require chronic opioid around-the-clock analgesia for moderate to severe pain; patients have been counseled about the risks and benefits and appropriate use of OxyContin, and about the risk of overdose due to giving OxyContin to

someone for whom it has not been prescribed; patients have been provided and reviewed the Medication Guide; and patients have been instructed that OxyContin tablets are to be swallowed whole and are not to be broken, chewed, or crushed because taking broken, chewed, or crushed OxyContin tablets leads to rapid release and absorption of a potentially fatal dose of oxycodone.

(ii) Will provide a copy of the signed physician-patient agreement form to the sponsor.

(b) The sponsor will maintain a list of the patients who have been enrolled and verify patient enrollment to those needing to verify that a patient has been or has not yet been enrolled. The sponsor will provide a unique patient identifier when each patient is enrolled. Patient will always be tracked using this unique identifier so that the sponsor can monitor OxyContin prescribing for each patient.

(c) Pharmacies, practitioners, or healthcare settings who dispense OxyContin must document that the drug has been dispensed under the following safe use conditions:

(i) The pharmacy, practitioner, or healthcare setting has dispensed OxyContin only to enrolled patients, based on a valid prescription from a certified prescriber (enrolled patients and certified prescribers to be determined from a list maintained by the sponsor).

(ii) The pharmacy, practitioner, or healthcare setting has ensured that patients who are receiving the higher strengths (i.e., 60 mg and above) are opioid-tolerant.

(iii) The pharmacy, practitioner, or healthcare setting has counseled patients on appropriate product use.

(iv) The pharmacy, practitioner, or healthcare setting has provided each patient a Medication Guide with each prescription and instructed the patient to read it.

Implementation System: The REMS must include an implementation system to monitor and evaluate the implementation of the elements to assure safe use (outlined above) that require that the drug be dispensed to patients with documentation of safe-use conditions. Include an intervention plan to address any findings of non-compliance with elements to assure safe use and to address any findings that suggest an increase in risk.

The Implementation System must include:

- A database of all enrolled entities including prescribers, pharmacies, practitioners, healthcare settings, and patients.
- A plan to monitor distribution data and prescription data to ensure that only certified pharmacies, practitioners, and healthcare settings are distributing and dispensing OxyContin and that only certified prescribers are prescribing OxyContin
- A plan to monitor and conduct audits of certified pharmacies, practitioners, and healthcare settings to ensure these entities are only dispensing OxyContin after documenting safe use conditions.

Timetable for Assessment: The proposed REMS should include a timetable for assessment that shall be no less frequent than every six months for the first two years, and

annually thereafter once the REMS is initially approved. We recommend that you specify the interval that each assessment will cover and the planned date of submission to the FDA of the assessment. We recommend that assessments be submitted within 60 days of the close of the assessment interval.

Each assessment must assess the extent to which the elements to assure safe use of your REMS are meeting the goals of your REMS and whether the goals or elements should be modified.

In accordance with section 505-1, within 60 days of the date of this letter, you must submit a proposed REMS and a REMS supporting document. The REMS, once approved, will create enforceable obligations.

We suggest that your proposed REMS submission include two parts: a "Proposed REMS" and a "REMS Supporting Document." Attached is a template for the Proposed REMS that you should complete with concise, specific information (see Appendix A). Include information in the template that is specific to your proposed REMS for OxyContin. Additionally, all relevant proposed REMS materials including enrollment forms, informed consents, and educational and communication materials should be appended to the proposed REMS. Once FDA finds the content acceptable, we will include this document as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS Supporting Document should provide a thorough explanation of the rationale for and supporting information about the content of the proposed REMS and should include the following sections as well as a table of contents:

1. Background
2. Goals
3. Supporting Information on Proposed REMS Elements
   a. Medication Guide and/or Package Insert
   b. Communication Plan
   c. Elements to Assure Safe Use
   d. Implementation System
   e. Timetable for Assessment of the REMS
4. Information Needed for Assessments
5. Other Relevant Information

Information needed for assessment of the REMS may include but may not be limited to:

1. A survey of patients' or healthcare providers' understanding of the serious risks of OxyContin
2. A report on the status of the training and certification program for healthcare professionals
3. A report on the status of patient enrollment.
4. An evaluation of the effectiveness of the REMS program through:

- a claims study to evaluate OxyContin utilization patterns including opioid-tolerant utilization patterns before and after implementation of your REMS
- an analysis and summary of surveillance and monitoring activities for abuse, misuse and overdose, and any intervention taken resulting from signals of abuse, misuse and overdose

5. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
6. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

Prominently identify the amendment containing the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

NEW SUPPLEMENT FOR NDA 20-553 [assigned #] PROPOSED REMS

Prominently identify subsequent submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

SUPPLEMENT[assigned #]
PROPOSED REMS – AMENDMENT

If you have any questions, call Lisa Basham, Regulatory Project Manager, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, MD
Director
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Attachment

Attachment A

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name
Address
Contact Information

PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide or PPI

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Communication Plan

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Append the printed material and web shots to the REMS Document

C. Elements To Assure Safe Use

List elements to assure safe use included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:

A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS ;

C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);

D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;

E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or

F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

D. Implementation System

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B),(C), and (D), listed above .

E. Timetable for Submission of Assessments

Specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments at a minimum must include an assessment by 18 months, 3 years, and in the 7th year after the REMS is initially approved, with dates for additional assessments if more frequent assessments are necessary to ensure that the benefits of the drug continue to outweigh the risks.

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/s/

Bob Rappaport
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